REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claims remain under examination in the application, is presented, with an appropriate defined status identifier.

Claims 1-13 were cancelled in the transmittal of the new application, filed on December 7, 2001. Thus, the first page of the Office Action, indicating that claims 1-13 are withdrawn from consideration, is incorrect.

In the present amendment, claims 77-92, which were withdrawn from consideration in response to a restriction requirement, have been cancelled. Applicants reserve the right to prosecute the subject of the cancelled claims in this or another application.

In addition, claims 14, 93, and 95 have been amended, and claims 102-110 have been added to the application. Claims 14, 93, and 95 have been amended to state that the compositions, and methods of using such compositions, do not comprise a phospholipid. New claims 102-110 recite the compositions of claims 14, 27, 39, 51, and 64 having: (1) a secondary non-cationic surface stabilizer (page 26, lines 8-9, of the application); and (2) specific particle sizes page 26, line 32, through page 27, line 5, of the application).

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Summary of the Claimed Invention

The claimed invention, as amended, is directed to bioadhesive compositions of nanoparticulate active agents and methods of using the same. The active agent particles, or

liquid droplets comprising active agent, have an effective average particle size of less than about 4 microns.

In a first embodiment, the compositions comprise: (a) a water-soluble or poorly water-soluble nanoparticulate active agent, which are in a crystalline state; and (b) at least one cationic primary surface stabilizer (claims 14-26, 98, 101, and 102). These compositions do not comprise a phospholipid.

In a second embodiment, the compositions comprise: (a) water-soluble or poorly water-soluble active agent particles which are in a liquid state at or near room temperature; and (b) at least one cationic primary surface stabilizer, wherein the active agent particles are dispersed in a liquid medium in which they are poorly soluble (claims 27-50 and 103-106).

In a third embodiment, the compositions comprise: (a) active agent dissolved or dispersed in liquid droplets of a water-soluble or poorly water-soluble liquid; and (b) at least one cationic primary surface stabilizer adsorbed to the surface of the liquid droplets, wherein the liquid droplets are dispersed in a liquid medium in which they are poorly soluble (claims 51-76, 99, and 107-110).

Finally, the invention encompasses methods of using the nanoparticulate active agent compositions of the invention. A first and second method encompass applying a nanoparticulate active agent formulation to a biological surface. The active agent particles of the first method can be in a semi-crystalline state, an amorphous state, a mixture of crystalline and semi-crystalline, a mixture of crystalline and amorphous, or a mixture of crystalline, semi-crystalline, and amorphous (claim 93 and 94). The active agent particles of the second method are in a crystalline state (claims 95 and 96). The compositions of these two methods do not comprise a phospholipid. A third method encompasses applying a nanoparticulate composition comprising agriculturally active agent particles to plant tissue.

The claimed invention satisfies a need in the art for effective, stable compositions having excellent adhesion properties to biological surfaces. The term "bioadhesion" refers to any attractive interaction between two biological surfaces or between a biological and a synthetic surface. In the case of bioadhesive nanoparticulate active agent compositions, the term bioadhesion is used to describe the adhesion between the nanoparticulate active agent compositions and a biological substrate (*i.e.*, gastrointestinal mucin). Application at page 13, lines 26-29. Surprisingly, the bioadhesive property of the compositions of the invention diminishes as the particle size of the active agent increases. *Id.*

The bioadhesive nanoparticulate active agent compositions are useful in any situation in which it is desirable to apply an active agent to a biological surface. For example, the bioadhesive nanoparticulate active agent compositions of the invention can be used in pharmaceuticals, including biologics such as proteins and peptides, organic compounds, such as therapeutic small molecules, agricultural agents, cosmetic agents, hair compositions, and others. The bioadhesive nanoparticulate active agent compositions of the invention coat the targeted surface in a continuous and uniform film which is invisible to the naked human eye.

The bioadhesive compositions can be applied to any plant or animal surface. The adhesion exhibited by the inventive compositions means that the active agent nanoparticles are not easily washed off, rubbed off, or otherwise removed from the biological surface for an extended period of time.

III. Obviousness-type Double Patenting Rejection

Claims 14-76 and 93-100 were rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-27 of U.S. Patent No. 6,428,814 B1. Office Action at page 3. Applicants respectfully traverse this ground for rejection.

The present application is a division of Application No. 09/414,159, filed on October 8, 1999, which issued as U.S. Patent No. 6,428,814 B1. In a Restriction Requirement for the parent application, mailed on December 19, 2000, the original claims of the application were

restricted into fourteen groups. Applicants elected for prosecution in the parent application Group I, claims 1-13. Claims 1-27 of U.S. Patent No. 6,428,814 B1 correspond to the subject matter of original claims 1-13.

Because the U.S. Patent and Trademark Office held in the parent application that the subject matter of original claims 1-13 is patentably distinct from the subject matter of original claims 14-76 and 93-100 being prosecuted in the present application, the USPTO is now estopped from asserting that the subject matter of claims 14-76 and 93-100 is *not* patentably distinct from the subject matter of original claims 1-13. *See e.g.*, MPEP § 804 ("Obviousness-type double patenting requires rejection of an application claim when the claimed subject matter is **not patentably distinct** from the subject matter claimed in a commonly owned patent . . .) (emphasis in original). *See also* MPEP § 806 ("Where restriction is required by the Office double patenting cannot be held . . .); and MPEP § 804.01 (The third sentence of 35 U.S.C. 121 prohibits the use of a patent issuing on an application with respect to which a requirement for restriction has been made, or on an application filed as a result of such a requirement, as a reference against any divisional application, if the divisional application is filed before the issuance of the patent.")

Accordingly, withdrawal of this ground for rejection is respectfully requested.

IV. Claim Rejections Under 35 U.S.C. § 103

A. Pace et al., U.S. Patent No. 6,177,103

Claims 14, 15, 17-21, 23, 24, 26, 27, 29-32, 34, 36, 37, 39-46, 48, 49-52, 54-59, 61, 62, 64, 66-72, 74, 75, 93, and 95 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over Pace et al., U.S. Patent No. 6,177,103 ("Pace"). Office Action at pages 4-5. Applicants respectfully traverse this ground for rejection.

1. Summary of Pace

According to the Examiner, Pace "teaches preparing a nanoparticulate composition of less than 2000 nm by adsorbing a cationic agent onto the surface of active agent particles . . ." Office Action at page 4.

Pace refers to submicron particles of water-insoluble compounds, particularly drugs, prepared by simultaneously stabilizing microparticulate suspensions of the compounds with surface modifier molecules by rapid expansion into an aqueous medium from a compressed solution of the compound and surface modifiers in a liquefied gas. *See* Abstract and col. 5, lines 14-21, of Pace. Examples of suitable surface modifiers include cationic surfactants. The objective of Pace is to "develop a process with high productivity based on the use of liquefied gas solvents, including supercritical fluid technology, that yields surface modifier stabilized suspensions of water insoluble drugs . . ." Pace at col. 4, lines 63-67.

2. The Invention of Claims 14-26, 95, 96, 98, 101, and 102

The invention of claims 14-26, 95, 96, 98, 101, and 102 is directed to a bioadhesive nanoparticulate active agent composition and a method of applying such a composition to a biological surface. The composition comprises a water-soluble or poorly water-soluble nanoparticulate active agent, which is in a crystalline state, and at least one cationic primary surface stabilizer. These compositions do not comprise a phospholipid.

In contrast to the claimed invention, Pace does not teach compositions comprising *crystalline* particles. The method of Pace requires "very fast precipitation" (col. 4, line 31) and "very rapid precipitation" (col 4, line 33). It is known to those skilled in the art that very rapid precipitation is the preferred way to produce amorphous particles, primarily because the molecules in solution don't have time to organize themselves into a crystalline lattice if the timescale for precipitation is very short. Moreover, Pace teaches that inhibition of crystalline formation is preferred. *See e.g.,* col. 4, lines 38-40 of Pace ("A rapid intimate contact between the surface modifier and the newly formed particle substantially inhibits the crystal

growth of the newly formed particle". For at least these reasons, Pace does not teach or suggest the invention of claims 14-26, 95, 96, 98, 101, and 102.

3. The Invention of Claims 27-38, 103, and 104, Requiring the Presence of Poorly Water-soluble Active Agent Particles Which are in a Liquid State at or Near Room Temperature, is not Taught or Suggested by Pace

The invention of claims 27-38, 103, and 104 is directed to a bioadhesive nanoparticulate active agent composition comprising poorly water-soluble active agent particles which are in a liquid state at or near room temperature and at least one cationic primary surface stabilizer. The active agent particles are dispersed in a liquid medium in which they are poorly soluble.

This subject matter is not taught or suggested by Pace, as Pace does not teach or suggest compositions comprising "poorly water-soluble active agent particles which are in a liquid state at or near room temperature," as required by Applicants' claims. For at least this reason, withdrawal of this ground for rejection against claims 39-50 is respectfully requested.

4. The Invention of Claims 39-50, 105, and 106, Directed to Compositions Comprising Water Soluble Active Agents, is not Taught or Suggested by Pace, Which is Limited to Poorly Water Soluble Active Agents

Claims 39-50 are directed to bioadhesive nanoparticulate compositions comprising *water-soluble* active agent particles, which are in a liquid state at or near room temperature, in combination with at least one cationic surface stabilizer. This is not taught or suggested by Pace, as Pace is strictly limited to compositions of poorly water soluble drugs. Nowhere in Pace does the reference suggest or teach compositions comprising water soluble active agents. For at least this reason, withdrawal of this ground for rejection against claims 39-50 is respectfully requested.

5. The Invention of Claims 51-63, 107, and 108

The invention of claims 51-63, 107, and 108 is directed to a bioadhesive nanoparticulate active agent composition comprising active agent dissolved or dispersed in liquid droplets of a poorly water-soluble liquid and at least one cationic surface stabilizer. The liquid droplets comprising active agent are dispersed in a liquid medium in which they are poorly soluble.

In contrast to the invention of claims 51-63, 107, and 108, Pace only teaches compositions comprising *solid* particles. Specifically, pending claims 51-63, 107, and 108 pertain to liquid droplets which are dispersed in a liquid medium and have at least one cationic surface stabilizer. Thus, the cationic surface stabilizer is at the liquid-liquid interface. Pace only discloses solid particles. For instance, the x-axes on Figures 1 and 2 of Pace are labeled "Solid Particles," and Pace makes use of the words "precipitated" and "precipitation" in several places (col. 4, lines 20, 31, 33, and 52). Furthermore, the examples disclose only fenofibrate and cyclosporine particles, both of which are solids at room temperature.

Accordingly, as this reference does not teach or suggest compositions comprising liquid droplets, Pace does not teach or suggest the invention of claims 51-63, 107, and 108.

6. The Invention of Claims 64-76 and 109, and 110, Directed to Compositions Comprising Active Agents Dispersed in Liquid Droplets of a Water Soluble Liquid, is not Taught or Suggested by Pace

Pace describes making particulate compositions utilizing liquefied gas solvents, including supercritical fluid technology. Examples of useful liquefied gases are described at col. 6, lines 6-33, of Pace. None of the liquefied gasses are "water soluble", as in process of Pace, the compressed solution of the compound and surface modifiers in a liquefied gas are expanded into an aqueous medium. Such expansion is not possible if the liquefied gas is soluble in water (*i.e.*, an aqueous medium).

Thus, for at least this reason Pace fails to teach or suggest the invention of claims 64-76 and 109, and 110, and, therefore, withdrawal of this ground for rejection is respectfully requested.

7. The Invention of Claim 97, Directed to a Method of Applying an Agriculturally Active Agent to Plant Tissue, is not Taught or Suggested by Pace

The invention of claim 97 is directed to a method of applying an agriculturally active agent to plant tissue. Pace does not teach or suggest compositions comprising an agriculturally active agent, nor does Pace teach or suggest applying such compositions to plant tissue. For at least these reasons, Pace fails to teach or suggest the invention of claim 97, and, therefore, withdrawal of this ground for rejection is respectfully requested.

B. Pace in Combination with Liversidge et al., U.S. Patent No. 5,145,684

Claims 22, 28, 35, 47, 53, 60, 65, and 73 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Pace in combination with Liversidge et al., U.S. Patent No. 5,145,684 ("Liversidge"). Office Action at page 5. Applicants respectfully traverse this ground for rejection.

According to the Examiner, "Pace does not expressly teach that the composition further comprises an excipient or that water is used as the dispersion medium. Liversidge teaches that such composition can further comprise a carrier (excipient) and that the dispersion medium can be water." Office Action at page 5.

Liversidge does not remedy the deficiencies of Pace, noted above in Section IV.A. Because the cited references fail to teach or suggest every element of Applicants' claimed invention, withdrawal of this ground for rejection is respectfully requested.

C. Pace in Combination with Cutie, U.S. Patent No. 5,891,420

Claims 98-100 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Pace in combination with Cutie, U.S. Patent No. 5,891,420 ("Cutie"). Office Action at page 6. Applicants respectfully traverse this ground for rejection.

According to the Examiner, "Cutie teaches that triamcinolone acetonide is a known anti-inflammatory." Office Action at page 6.

This reference does not address the deficiencies of Pace and Liversidge, detailed above. For at least these reasons, withdrawal of this ground for rejection is respectfully requested.

V. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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